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Slings for urinary incontinence and the application of cell-based therapy ☆

Lukman Hakim [a,b], Dirk De Ridder [a,*], Frank Van der Aa [a]

[a] Department of Development and Regeneration, Urology, KU Leuven–University of Leuven, Herestraat 49, Leuven 3000, Belgium
[b] Faculty of Medicine, Department of Urology, Airlangga University/Dr Soetomo General Hospital, Mayjend Moestopo 6-8, Surabaya 60235, Indonesia

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ABSTRACT

The most commonly used technique for the treatment of stress urinary incontinence (SUI) in women is the suburethral polypropylene sling, using either a retropubic or transobturator tape approach This treatment results in a cure rate of over 80%, based on both subjective and objective evaluations. Biological slings have been largely abandoned due to lack of efficacy. Despite the high success rates, 10–20% of women remain incontinent.
Cell-based therapy might offer solutions for the future both for the primary setting as for the treatment of failures. Preclinical studies suggest that stem cells (SC) can enhance the recovery of damaged tissue either by direct integration and replacement of damaged tissue (differentiation) or by secreting factors that influence host response mechanisms (paracrine effect).
The clinical data to date do not allow strong efficacy conclusions, except that SC therapy seems to be safe in the short term. Most published studies use autologous cells. Allogeneic cell sources need to be investigated as well to allow ready-to-use solutions in the future.
Most importantly, we need better insight into the mechanisms of action. We need more basic stem cell research, better acute and chronic animal models, better investigational tools and more efforts using tissue engineering approach.

Contents

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* Corresponding author at: Department of Urology, KU Leuven–University Hospitals, Herestraat 49, Leuven 3000, Belgium. Tel.: +32 16346930; fax: +32 16346931.
E-mail addresses: lukman.hakim@uzleuven.be (L. Hakim), dirk.deridder@uzleuven.be (D. De Ridder), frank.vanderaa@uzleuven.be (F. Van der Aa).

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1. Introduction

The lifetime risk of pelvic floor surgery among women at 80 years old was 11.1% where 29% had at least one previous surgery [1]. More than 15 years later, the lifetime risk remained the same about 12.2%, where 6.2% women had at least one previous surgery of whom 19% had repeat operations. These results did not necessarily imply the reoperation rate for slings in incontinence patients. In the latter study, midurethral slings and periurethral injectables as initial urinary incontinence (UI) surgery have been considered as independent predictors for reoperation. Midurethral slings as initial surgery in UI patients were 70% less likely (HR = 0.3; 95% CI = 0.15–0.6; $p = 0.001$) to experienced reoperation, meanwhile periurethral injectables were 9-fold (HR = 9.05; 95% CI = 2.42–33.8; $p = 0.001$) more frequent to experienced reoperation following treatment. The reoperation rate for slings in incontinence patients was 3.2% in the Abdel-Fattah cohort, while it was 5% in our cohort. While surgeon in high-volume centers might play an important role in the significant decline of failure of pelvic floor surgeries, we believe that better mesh materials and surgical techniques nowadays contributed as well.

Sling surgery has become the surgical therapy of choice for stress incontinence in women. Slings can be classified according to their composition: autologous, heterologous, synthetic or to the surgical approach: pubovaginal or retropubic, transobturator (inside-out or outside-in) or single-incision mini-sling. Autologous sling is routinely used still in type 3 incontinence. Worldwide the number of Burch colposuspension is declining in favor of midurethral slings [2,3]. All of the sling surgery approaches have advantages and risks; therefore, it is important that the surgeon is aware of these aspects in order to counsel patients in an honest and reliable way. Despite the high success rate, synthetic sling surgeries are not without complications. Recurrence, urinary retention lasting more than 6 weeks, erosions, extrusions, groin pain, leg pain, bladder perforation, urethral perforation, vaginal perforation and deep vein thrombosis are complications that might occur [4]. Researchers have been focusing to investigate other treatment options than surgery that might address these issues, where cell-based therapy might play a role. Cell therapy might be a potential option to solve the underlying problem of SUI patients rather a symptom-relief approach.

2. Indications for sling surgery

SUI with urethral hypermobility is the standard indication for any sling. More complex conditions such as mixed incontinence (stress and urgency incontinence) might respond to sling surgery as well, but usually subsequent treatment for the urgency component will be necessary. Also recurrent incontinence after previous failed slings can be treated by secondary synthetic or autologous slings. For patients with intrinsic sphincter deficiency and severe incontinence, autologous sling can be positioned as a “tight” sling that compress the urethra. In these cases, intermittent catheterization will be necessary to ensure bladder emptying.

3. Autologous pubovaginal sling

The use of autologous material to support the bladder neck and urethra goes back more than 100 years [5]. When Burch colposuspension became more popular, the use of fascial slings was restricted to complex or failed cases. Burch suspension is a type of bladder neck suspension for stress urinary incontinence where the lateral vaginal fornices is fixed to the iliopectineal ligaments. From 1998, when the tension-free transvaginal tape (TVT) became widely available, fascial slings became nearly obsolete. In recent years, however, there is a renewed interest. Complications of synthetic slings such as erosion, perforation or obstruction often result in the partial or complete removal of the synthetic sling, leading to recurrent stress incontinence. In these cases, the traditional fascial slings seem to be used again to avoid the use of synthetic material [6].

The most common indications for an autologous pubovaginal sling are intrinsic sphincter deficiency with or without urethral hypermobility and a prior failed incontinence procedure. Also, certain patients with severe SUI due to urethral hypermobility may be better served with an autologous pubovaginal sling procedure because of the long-term success and durability of this sling. However, Jones et al. (2010) described that inform-consent pre-operatively should be made to patients that transvaginal tape (TVT) placement carries a risk potentially exceeding 4% of tape-related complications requiring further surgical intervention [7]. Options of treatment should me made thoroughly to patients to freely decide, regarding the potential complication that may occur.

4. Retropubic tension-free vaginal tape

Some developments have paved the way to the introduction of the revolutionary retropubic tension-free vaginal tape TVT in 1996. First, it was recognized that the functional restoration of the urethral closing mechanism was more important than the correction of the anatomy. The second development was the acknowledgement of the importance of the midurethra in the continence mechanism. This was supported by the discovery of the pubourethral ligaments, the observation that the maximum urethral closing pressure is located midurethrally and that, in continent women, the urethra closes in the middle part. Therefore, the new concept of the integral theory by Petros and Ulmsten stated that SUI was caused by a lacking midurethral closing mechanism. This could be caused by failure of the pubourethral ligaments, lacking support of the anterior vaginal wall to the midurethra or by defective functioning of the pubococcygeal muscles that support the adjacent part of the urethra. Connective tissue structures (ligaments) are regarded very important in the integral theory and therefore surgical treatments are aiming at restoring these ligaments.

5. Transobturator tapes

A new era of stress incontinence surgery started with the introduction of the TVT. This new classic gives support to the midurethra and prevents dislocation of the midurethra during intra-abdominal pressure rise. The midurethral tape is U-shaped and runs retropubically. The most frequently occurring complication is bladder perforation when the needles with the connected tapes pass behind the pubic bone. Since the bladder is in the vicinity, it is easily perforated. Therefore, urethrocystoscopy is recommended during the procedure. In order to avoid bladder perforation and urethrocystoscopy during the procedure, the transobturator approach was introduced by Delorme [8,9]. The transobturator tape (TOT) runs from one obturator foramen along the anterior vaginal wall via the midurethra to the opposite obturator foramen in a V-shaped fashion

6. Single-incision slings

Minimizing the size of the sling and reducing the number of incisions lead to the appearance of the so-called mini-slings. These single-incision slings are fixed with harpoon-like devices in the obturator muscle. Several types of these slings have been introduced and many of those lack good scientific data to support their use in the routine practice. The first mini-sling was the TVT-Secure. After initial enthusiasm, it rapidly became clear that the results were about 10% less than with standard transobturator or retropubic approaches. The TVT-Secure was withdrawn from the market in 2012, but the poor results continue to confound the systematic reviews and meta-analyses on mini-slings to date. A recent systematic review excluding the TVT-Secur data by Mostafa et al. [10] found no significant differences between data published on mini-slings and standard midurethral slings. The mini-slings showed an earlier recovery. These data should be interpreted with

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caution because of the heterogeneity of the included studies and the data only reflect midterm follow-up.

7. Which sling to choose?

Recently, a systematic review and meta-analysis was performed concerning sling surgery for SUI in women [11]. Based on the findings of randomized controlled trials, several conclusions could be drawn:

a. Midurethral slings versus Burch: No difference between objective cure, either intervention can be proposed but the decision should take into account potential adverse events and concomitant surgeries. Burch suspension is more invasive since laparotomy needs to be conducted to perform the fixation between the lateral vaginal fornices and the iliopectineal ligaments, therefore this approach should be considered only when concomitant surgery is necessary.
b. Autologous pubovaginal sling versus Burch: Subjective and objective cure are better in autologous pubovaginal slings.
c. Autologous pubovaginal sling versus midurethral sling: Subjective cure favors midurethral sling.
d. Obturator sling versus a retropubic sling: Adverse event analysis showed that urgency symptoms after surgery were common following a retropubic sling. Hence, both retropubic and obturator slings can be recommended but the decision should be balanced for adverse events, where TVT showed more evidence.
e. Mini-slings versus midurethral slings: Objective and subjective cure rate significantly favors midurethral slings.

The European Association of Urology guidelines, however, are slightly different, maybe due to the PICO methodology that was used in creating the guidelines [12]:

a. Midurethral slings should be offered to women with uncomplicated SUI as the initial surgical intervention
b. Colposuspension (open or laparoscopic) or autologous fascial sling should be offered to women with SUI if midurethral sling cannot be considered. Colposuspension is a surgery that involves the placement of permanent stitches at the level of the bladder neck, to lift up the bladder and correct the problem of stress urinary incontinence. This can be perform whether by open surgery or using minimal-invasive approach (laparoscopy). Meanwhile, in the autologous pubovaginal sling procedure, a support constructed of rectoabdominal fascia to stabilize the bladder neck from underneath is performed in order to treat SUI.
c. Women who are being offered a retropubic synthetic sling should be warned about the relatively higher risk of perioperative complications compared with transobturator insertion.
d. Women undergoing autologous fascial sling should be warned that there is a high risk of voiding difficulty and the need to perform clean intermittent self-catheterization; ensure they are willing and able to do so.
e. Women being offered a single-incision sling device, for which an evidence base exists, should be warned that they may be less effective than standard midurethral slings and that efficacy beyond 1 year remains uncertain. Single-incision sling devices without level 1 evidence of effectiveness should only be implanted as part of a structured research program.

8. Biological slings

Biological xenografts were introduced in the late nineties. Theoretically, they would yield less complications such as erosion or extrusions and the incorporation in the native tissue would be better. Pelvicol™ (cross-linked porcine dermis) and Intexen™ (non-cross-linked porcine dermis) were used in the treatment of SUI and of pelvic organ prolapse with variable results. The long-term success to treat SUI seemed to be inferior to standard synthetic slings. A recent RCT comparing Pelvicol slings with autologous pubovaginal sling and synthetic midurethral slings showed that after 1 year, the continence rate was only 63% for Pelvicol slings, while it was 90% for both autologous pubovaginal slings and midurethral synthetic slings [13]. It was also shown that these biomaterials did not integrate very well into the host tissue and lost tensile strength over time [14,15].

Small intestinal submucosa is another biomaterial that consists of decellularized porcine submucosa. Since a single layer of submucosa is difficult to handle and does not provide enough strength, multiple layers are used: 4- and 8-layer constructs are available. Again, after initial enthusiasm, the continence results proved to be disappointing [16,17]. Moreover, in several case reports, inflammatory reactions to this material have been described [17,18].

In general, the use of biological slings has faded in the recent years because of the aforementioned results, the doubts about long-term efficacy and the fear of transmittable diseases. The ease of use of the current synthetic slings, the good midterm and long-term results of these slings and the limited number of serious complications have made the use of biomaterial slings virtually obsolete.

9. Will cell-based therapy or tissue engineering provide benefit for the treatment of SUI?

Given the success of the synthetic slings one could wonder if there is anything to improve. The success rate of 85–90% implies that 15–10% of patients will have persisting incontinence despite having undergone sling surgery. Other patients will have had partial or complete sling removals for obstruction or for erosion and will need subsequent treatment for incontinence. A proportion of patients will also develop de novo urgency following sling surgery, which is not frequent but may invalidate pain. Hence, despite the fact that in the majority of patients sling surgery will lead to significant improvement or cure of the continence, major challenges for future research and product development lie ahead.

The development of the biological slings unfortunately did not really work. Two lines of research are now being followed. On the one hand, researchers try to design scaffolds that are seeded with cells and that can be used as tissue-engineered meshes that integrate in the host tissue. On the other hand, sphincter regeneration is being attempted by injecting a variety of stem cells into the sphincter zone, hoping that this will restore the function of the weakened sphincter muscle and support tissues (Fig. 1). Results of clinical trials using autologous tissue are awaited.

10. Regenerative medicine for the treatment of SUI

Up to date, the application of regenerative medicine for SUI has been dominantly focusing on cell therapy in order to restore the natural continence mechanism. The rationale behind this is that both conservative and surgical treatments for SUI ended with recurrences and/or complications in some patients in the long-term outcome, such as erosion, retention, retreatment false route, etc. These treatments are thought to focus more on relieving symptoms rather than treating the underlying disease.

Clinical trials for cell therapy in SUI are scarce, mainly due to ethical or regulatory reasons. If existing, they are limited to non-randomized studies with small sample size or even case reports. On the other hand, preclinical trials kept going on, showing a better understanding in the mechanism of action on how externally injected cells may restore the urethral function.

The role of tissue engineering for SUI has been increasingly studied in order to enhance cell therapy. Many preclinical studies exist and showed the benefit of combining additional substances to cell therapy for SUI treatment. Unfortunately, this approach has not been brought into the clinical setting.

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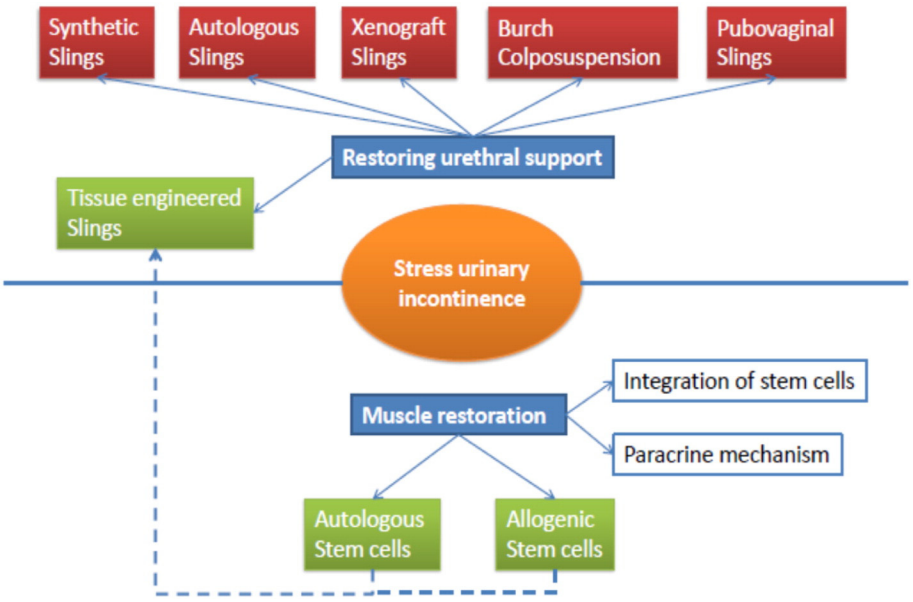

Fig. 1. A graphical abstract of different approaches for the treatment of stress urinary incontinence. In the clinical setting, surgical efforts have been introduced to restore the urethral support in SUI patients using different approach and mesh materials: synthetic slings, autologous slings, xenograft slings, Burch colposuspension and autologous pubovaginal slings. The role of cell therapy has been introduced in the preclinical settings in order to restore both skeletal and smooth muscles of the external urethral sphincter, using both autologous and allogenic stem cells. Paracrine factors has been shown to be responsible for the migration of stem cells to the site of injury, while lack of evidence showed the integration of these cells into the muscles. The use of stem cells for tissue engineering has also been introduced to restore the urethral support.

10.1. Cell therapy for SUI: the bench side

The advantage of injecting muscle-derived stem cells (MDC) over the injection of fibroblast in the damaged sphincter was shown by Kwon et al. [19]: both MDC and fibroblast injection increased the LPP in an SUI rat model but only MDC significantly improved urethral muscle strip contractility. Moreover, urinary retention developed with high-dose fibroblast injection, but not with MDC injection.

In the preclinical setting, multipotent mesenchymal stem cells (MSC) present in adults in most of the tissues derived from mesoderm have been mostly used for SUI. Different types of stem cells have been applied: skeletal muscle derived (myoblasts, satellite cells, muscle progenitor cells and muscle-derived stem cells), bone marrow stem cells (BMSC), human umbilical mononuclear cells, adipose-derived stem cells (ADSC) and modified/sorted stem cells which show various efficacy [20]. These cells have been proven to demonstrate nerve regeneration and improve musculature profiles of the external urethral sphincter, which lead to functional improvement. Paracrine factors have been thought to be responsible for the improvement rather than cellular differentiation [21]. Lin et al. (2010) observed possible differentiation of ADSC into smooth muscle of a vaginal dilatation (VD) model following intravenous ADSC injection by the appearance of Edu (5-ethynyl-2′-deoxyuridine)-positive nuclei localized within cells that stained positive for alpha-smooth muscle actin (α-SMA) [22]. Mesenchymal stem cells and $CD34^+$ have been proven to differentiate into muscular and vascular components. On the other hand, the use of cytokines and growth factors such as hipoxia-induced factor-1, vasculo-endothelial growth factor, basic fibroblast growth factor and insulin-like growth factor have shown to enhance the viability and direction of stem cell differentiation [23]. More recently, Dissaranan et al. showed that mesenchymal stem cells migrate to the urethra and vagina and facilitate recovery of continence most likely via secretion of paracrine factors. The authors also showed that intravenously injected MSCs preferentially engraft in the smooth muscle of urethra and vagina based on histological analysis and confocal imaging. Both MSCs and the conditioned culture medium the authors use showed promising results [24,25].

Among these type of cells, ADSC have the advantage of being abundantly available and of being easy to prepare. This leads to a shorter preparation time prior to its use and thus makes them more suitable for clinical application. Unlike bone marrow-derived cells, ADSC would less likely cause morbidity when harvested from humans. Although novel sources of stem cells have been introduced for urologic applications such as placental and amniotic fluid stem cells, urine-derived stem cells and umbilical cord-derived stem cells, none of these have been applied for SUI treatment [26].

In terms of efficacy, the use of stem/progenitor cells treatment for SUI has reached a major step nowadays, by the fact that it has been brought it into the clinical setting. Some clinical trials have shown promising results for the treatment of SUI [27–29].

Unfortunately, some drawbacks exists in preclinical trials at this moment.

First, vaginal distension and pudendal nerve injury models in rodents that have been commonly used to simulate SUI in women are acute models in nature, while SUI in women is a chronic symptom [30–37]. The question rises whether stem cell applications in these models should or could be used as curative-intent treatments or if they should be considered as preventive treatments (e.g., injecting cells after vaginal delivery to prevent future SUI).

The choice of an adequate preclinical model is difficult. Next to rat models, canine models have been described [38]. Other models such as nonhuman primates might be more relevant to the human situation, but the use of these models is obviously limited. Despite these limitations, Badra et al. [39] showed nicely that muscle-derived stem cell integrated well in the sphincter system after pudendal nerve injury in cynomolgus monkeys and that this also resulted in a better sphincter function.

Second, current models are in general not durable and tend to recover spontaneously in a short period, unlike SUI in women. Efforts were made to develop a more durable model by the combination of methods of injury, longer time of injury and/or using additional substances to prolong the natural recovery of these models [40–45].

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Third, most of the previous studies have only observed improvement in musculature of the EUS following stem cells injection based on histological examination. These histological images, however, might just show transplanted stem cells and are not a proof of functional integration. Unfortunately, not many of these studies could identify the differentiation of stem cells [20].

Fourth, the best delivery method of stem cells still needs to be investigated. While transurethral injection of stem cells was employed almost exclusively in clinical trials, periurethral injection was used in all preclinical trials. Intravenous injection was also used in one preclinical study [20]. Du et al. showed that BMSC, muscle-like cells and calcium alginate composite gel have the potential to differentiate into muscle cells in the microenvironment of an SUI rat model. However, longer observation time is still needed to further induce myoblast proliferation to form a more complete muscle cell structure and gradually replace the gel to provide sufficient support for the urethra. In addition, the control of alginate gel porosity, the best combination ratio of the gel with stem cells or muscle-like cells, the best time, cytokines, growth factors and other factors, may affect cell proliferation and the formation of muscle fiber by tissue engineering and these issues need to be studied further [46].

10.2. Limitations in the method of assessment of SUI models

Different methods to determine SUI in lab animals have been used, most commonly leak point pressure (LPP) and electromyography of the external urethral sphincter (EUS EMG) [47–49]. These methods provide limitations since LPP requires a learning curve before stable results can be achieved. Also, LPP measurements are possible inconsistent regarding the bladder volume since its emptiness was not confirmed prior to measurements.

EUS EMG is invasive and traumatic due to concentric needle placement and potentially induces a bias due to noise of the raw EMG signals.

Recently, high-frequency microultrasound (μ US) has been introduced as a reproducible method to assess urethral function in female rats following simulated birth injury [50]. The authors showed that μUS could be used to assess EUS bursting during the 2nd-phase of micturition cycle using predetermined parameters: interburting interval (IBI) and length of bursting (LOB). Uninjured rats showed a rhytmic pattern of EUS bursting, while none of the VD rats showed EUS bursting during urine leakage.

Furthermore, in a subsequent study, the same group validated μUS to EUS EMG, which has been considered as the gold standard to assess urethral function. Simultaneous measurement of cystometography (CMG), μUS and EUS EMG in 15 nulliparous-uninjured rats at different saline-infusion rates of 5, 10 and 60 ml/h was performed. No significant differences of IBI and LOB were found when μUS and EUS EMG was compared within group of different infusion rates (Fig. 2). Meanwhile, μUS or EUS EMG showed no significant differences of IBI and LOB when measured at different infusion rates (Fig. 3). However, all parameters of CMG (baseline pressure, BP; threshold pressure, TP; peak pressure, PP) tend to increase as the infusion rate increases. The rate of bursting (ROB) remains stable while the total length of each bursting (TLB) became longer as the infusion rates increases, indicating that rats void at a longer time but with consistent rate of bursting (Fig. 3). In summary, the authors concluded that both EUS EMG and μUS could be used to assess urethral function with consistent results at different infusion rates. μUS is advantageous to EUS EMG and LPP as being less-operator dependent, non-invasive, no bias possibilities due to raw signals and fewer animals needed for experiments. (See Fig. 4.)

Therefore, at this point, the preclinical study of stem cells for SUI remains important and further studies need to be conducted emphasizing on developing a durable model of SUI, a reproducible method to determine SUI, the mechanism of stem cells action, the differentiation of applied cells, the optimum dosage, the most efficacious type of cells and the route of injection. In any event, stem cell transplantation appears to be a promising treatment for SUI [45].

10.3. Cell therapy for SUI: at the bedside

Unlike the application for non-urological diseases such as cardiology, randomized double-blind clinical trials for SUI in humans are scarce and involve small sample sizes. Moreover, most of the available studies did not provide empirical data, not allowing to draw any sound conclusion [51]. Two of them were even retracted due to ethical and undisclosed reasons.

Also different methods have been used to transplant the cells of interest in these studies. Transurethral or periurethral delivery under ultrasound or cystoscopy guidance have been used but the optimal technique remains to be elucidated.

Cell therapy for SUI has been initiated by Chancellor et al. (2000) in a preclinical trial which studied the role of intraurethral injection of myoblasts to enhance the urethral wall coaptation and to possibly improve the urinary sphincter function [52]. This methodology is now being investigated in a American/European multicenter study.

Mitterberger et al. (2007) had so far provide the largest-sample size ($n = 123$) of cell therapy in women with a follow-up of 1 year. The authors observed a complete improvement in 79% of women 36–84 years of age, 13% of substantial improvement and 8% of slight improvement following autologous injection of fibroblast and myoblast derived from skeletal muscle [53]. This group, however, had to withdraw their publications because of ethical issues. The composite continence score they developed to show this success rate is no longer used and the highly favorable results cannot be trusted.

Some other studies showed cure rate between 40% and 75% [54–56].

Sèbe et al. [54] injected 12 women with persistent SUI after failed surgery with muscle-derived stem cells. While the quality of life improved in 50% at 3 months time, 3 patients became dry, 7 improved and 2 worsened.

Carr et al. [55] injected 8 women with SUI of whom 3 withdrew from the trial early. Of the 5 remaining patients, one achieved continence while the others showed some improvement. Importantly, they noted that the onset of improvement was only after 3–8 months.

The same author also published a dose finding study [56]. A total of 38 women underwent intrasphincteric injection of low doses (1, 2, 4, 8 or 16×10^6) or high doses (32, 64 or 128×10^6) of autologous muscle-derived cells (AMDC). Intrasphincteric injection of AMDC in these doses seemed to be safe. Additionally, efficacy data suggested a trend toward greater efficacy with doses of 32×10^6 AMDC or greater.

Lee et al .[56] used umbilical cord stem cells in 39 women with SUI. He showed subjective improvement in 72% at 1 year. They also noted a progressive improvement over time since more patients were cured at 12 months than at 3 or 6 months. However, this study has major methodological flaws and should be interpreted with caution.

Blaganje et al. [57] injected autologous muscle-derived stem cells in 38 women with SUI. Initially the women were treated with electrical stimulation alone for 6 weeks. Then the stem cells were injected, and another 6 weeks of electrical stimulation were given. At the end of this 6-week period, 5 women were cured and 29 improved. Unfortunately, there was no control group.

Kuismanen et al. [58] injected 5 women with ADSC of whom 1 became continent after 6 months and 2 more at 12 months, using the cough stress test as outcome measure.

So far, no randomized controlled data are available, nor are there any long-term data. Next to the lack of good data, a health-economic analysis will be needed to establish the potential role of this therapy in the future. Dosage of cells injected, number of injection and the method of delivery are other factors that need to be addressed in a future study.

However, at this moment, the clinical trials that have been conducted in humans have at least provided evidence that stem cells for SUI are safe in the short term and that the effect of the injected cells only becomes apparent after a few months. Efficacy needs to be elucidated further since some number of studies showed clinical improvement but some others not [51].

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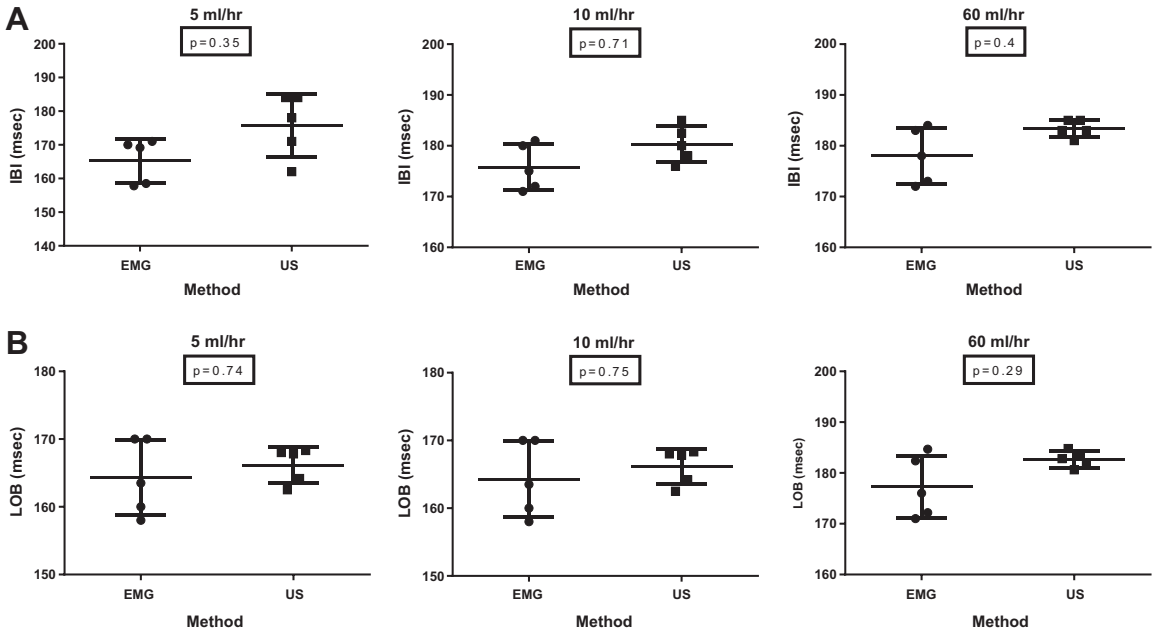

Fig. 2. One-second intraburst analysis comparing EUS EMG and μUS measurements at different infusion rates of 5, 10 and 60 ml/h. The IBI did not show significant differences at 5, 10 and 60 ml/h when EUS EMG and μUS results were compared ($p = 0.35$, $p = 0.71$ and $p = 0.4$, respectively). Similar results were shown for LOB ($p = 0.74$, $p = 0.75$ and $p = 0.29$, respectively).

10.4. Tissue engineering trials

The role of tissue engineering for the treatment of SUI started with the idea that addition of cytokines and/or growth factors may enhance the viability and direction of stem cells differentiation. Practically, the application of tissue engineering can be classified as the use of cell-growth supporting substances and/or materials (bio-compounds) to enhance cell therapy including the use of slings and/or scaffolds.

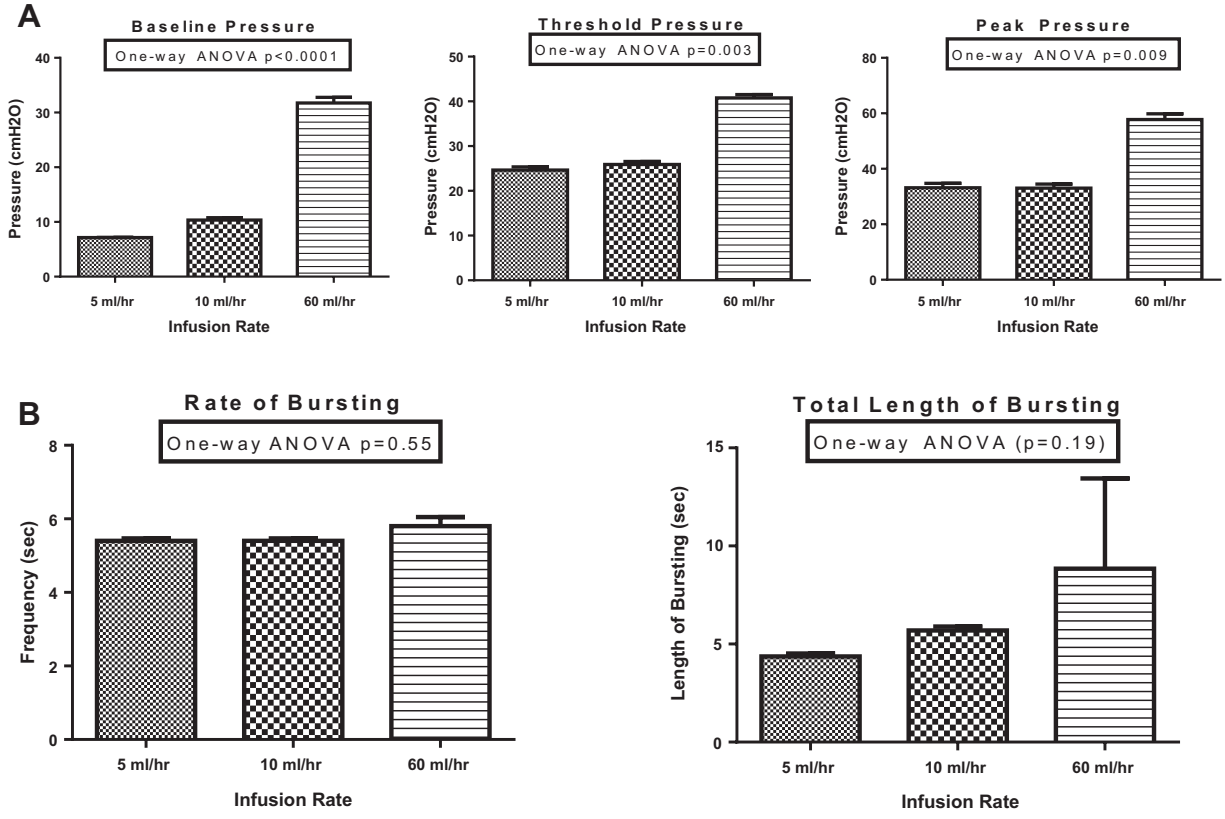

Fig. 3. A bar chart of voiding analysis. (A) Voiding analysis showed baseline pressure (left, BP), threshold pressure (middle, TP) and peak pressure (Right, PP) at different infusion rates of 5, 10 and 60 ml/h. These parameters tend to increased significantly as the infusion rate increases.(B) The ROB showed consistent results with no significant differences when different infusion rates were applied ($p = 0.55$); meanwhile, the TLB tend to be higher as the infusion rates increases ($p = 0.19$).

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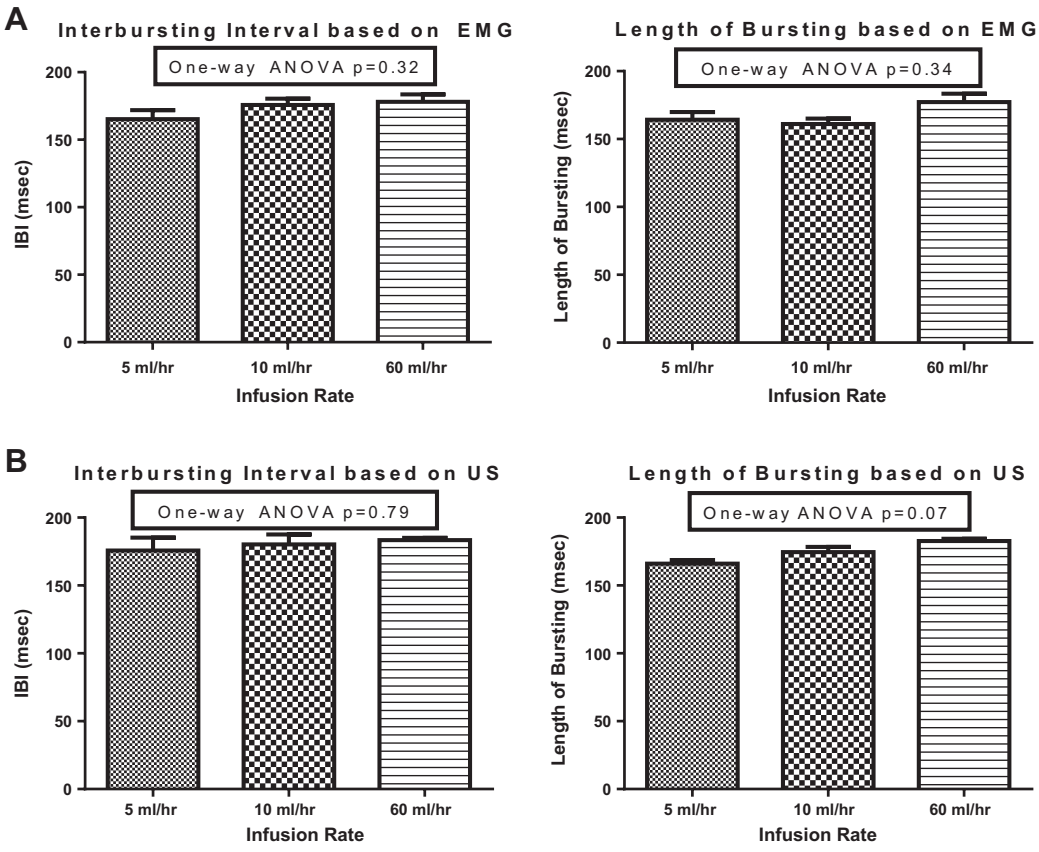

Fig. 4. A bar chart of intraburst analysis at different infusion rates. (A) The IBI ($p = 0.32$) and LOB ($p = 0.34$) based on EUS EMG did not differ significantly when different infusion rates were applied. (B) Similar results were observed for IBI ($p = 0.79$) and LOB ($p = 0.07$) based on μUS measurement.

Bioengineered degradable scaffolds are one example for this. Such scaffolds may release growth factors upon degradation in a controlled and predictable manner, thus enhancing recovery or stem cell differentiation. The use of mesh in scaffolds can be in general divided into non-absorbable mesh and absorbable mesh types. The latter was meant to be absorbed with an adequate tensile strength until the cells grow and pick up a blood supply, thus mimicking the use of autologous fascia.

Zou et al. [59] compared an acellular silk sling with a sling seeded with BMSCs and observed a better integration in the cell seeded group between the silk sling and the native urethral structure at 12 weeks following injury of the sciatic nerve. The BMSCs-seeded silk sling group in this study showed a double-increase of collagen fiber formation with a higher Young's modulus as compared to non-seeded group, suggesting that the continence mechanism improved.

Meanwhile, Zhao et al. [60] seeded ADSCs onto poly-lactic-co-glycolic acid (PLGA; synthetic scaffold) microparticles containing nerve growth factor (NGF) and injected them periurethrally following bilateral pudendal nerve transsection in female rats. The authors showed improvement of continence mechanism by an increase of LPP compared to groups without PLGA and/or NGF. The study also emphasized the role of NGF to prolong the survival of ADSCs. This enhanced the urethral smooth muscle profile and increased the density of neurofilaments in the sphincter lamina propria, thus increasing the urethral resistance.

Various kinds of scaffolds have been proposed. Poly-1,8-octanediol-co-citrate (POC) has been studied by Sharma et al. to promote angiogenesis and increase vascular growth [61]. The addition of heparin sulfate that bound to growth factors prevented the enzymatic degradation, which in turn improved tissue healing [61]. Although potentially useful, this scaffold has not been studied for SUI in the preclinical setting.

Recently, Shi et al. (2013) developed a tissue-engineered bulking agent consisting of ADSCs and silk fibroin microspheres (SFM) to treat SUI and injected them periurethrally in bilateral pudendal nerve-transected rats. The SFM improved urethral resistance as showed by the increasing LPP at a short-term period (4 weeks following injury), but its efficacy disappeared by 8 and 12 weeks. Conversely, when ADSCs were seeded with SFM, recovery of LPP could still be observed up to 8 and 12 weeks, thus providing a longer-term efficacy.

Cannon et al. [62] used a small intestine submucosa sling in a rat model of SUI following bilateral proximal sciative nerve denervation. One group was implanted with the sling, while the other group was implanted with a sling seeded with muscle-derived cells. The results showed no advantage of adding cells.

The production of scaffolds and the attachment of oral fibroblasts and ADSC to these scaffolds has been studied extensively by Roman et al. [63,64]. Further studies on the host response to these constructs are awaited.

In the future, we believe that tissue engineering strategies will be increasingly applied in order to enhance cell therapy and to improve sling properties.

11. Conclusion

The gold standard in the treatment of SUI in women is the suburethral macroporous polypropylene sling by a retropubic or transobturator approach. Most slings result in a cure rate of more than 80% that is maintained for a long time, although some evidence showed potential surgical complications mini-slings are still being evaluated. Their role remains to be elucidated. Biological slings proved to yield inferior results and have been largely abandoned.

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For patients with persistent incontinence after sling surgery, a secondary sling might be an acceptable options. Despite the high success rates, 10–20% of women continue to be incontinent. Also, sling erosion, obstructive voiding and persistent pain are possible complications of sling surgery.

Cell-based therapy and tissue engineering for SUI might be a solution for the future [65].

Preclinical studies suggest that stem cells can differentiate into smooth muscle cells and that they can enhance the recovery of damaged tissue by integration and replacement of damaged tissue. On the other hand, a paracrine mechanism of action, by secreting factors that modulate local responses to the damage, has been shown. Modifying sling properties using tissue engineering seems promising as well.

The paucity of clinical data and the poor design of the few clinical trials do not allow drawing any sound conclusions at this moment. Most of these studies use autologous cells, meaning that there will be a time delay between the harvesting of the cells and the re-injection after cell sorting and expansion. Allogeneic cell sources could avoid this drawback and need to be investigated to allow ready-to-use solutions in the future.

However, most importantly, we need better insight in the mechanism of action of cell-based therapy for SUI. Therefore, we need more basic stem cell research, a better understanding of the tissue changes after chronic pelvic floor dysfunction, better acute and chronic, animal models, better investigational tools and more effort into tissue engineering.

Disclosures

Lukman Hakim does not have any conflict interests to declare.
Dirk De Ridder: American Medical Systems.
Frank Van Der Aa: proctor for American Medical Systems.

References

[1] A. Olsten, V. Smith, J. Bergstrom, J. Colling, A. Clark, Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence, Obstet. Gynecol. 1989 (4) (Apr 1997) 501–506.
[2] C.J. Wu, Y.C. Tong, S.M. Hsiao, C.C. Liang, S.J. Liang, S.F. Weng, et al., The surgical trends and time-frame comparison of primary surgery for stress urinary incontinence, 2006–2010 vs 1997–2005: a population-based nation-wide follow-up descriptive study, Int. Urogynecol. J. 25 (2014) 1683–1691 (2014/06/29 Ed.).
[3] S.Y. Cho, S.J. Jeong, J.K. Yeo, S.O. Kim, J. Jeong, J.B. Choi, et al., Nationwide database of surgical treatment pattern for patients with stress urinary incontinence in Korea, Int. Neurourol. J. 18 (2) (2014) 91–94 (2014/07/06 Ed.).
[4] M.O. Schimpf, D.D. Rahn, T.L. Wheeler, M. Patel, A.B. White, F.J. Orejuela, et al., Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis, Am. J. Obstet. Gynecol. 211 (1) (Jul 2014) 71.e1–71.e27 (Internet, cited 2014 Oct 14, Available from: http://www.ncbi.nlm.nih.gov/pubmed/24487005).
[5] R. Goebel, Zur operativen Beseitigung der Angelborenen incontinenz vesicae, Z. Gynakol. Urol. 2 (1910) 187–190.
[6] J.C. Hou, G.E. Lemack, The role of fascial slings in the treatment of stress urinary incontinence in women: a 2013 update, Curr. Urol. Rep. 14 (3) (2013) 247–252 (2013/03/12 Ed.).
[7] R. Jones, P. Abrams, P. Hilton, K. Ward, M. Drake, Risk of tape-related complications after TVT is at least 4%, Neurourol. Urodyn. 29 (1) (2010) 40–41.
[8] E. Delorme, Transobturator urethral suspension: mini-invasive procedure in the treatment of stress urinary incontinence in women. Prog. Urol. 11(6):1306–13.
[9] E. Delorme, Transobturator tape (Uratape). A new minimally invasive method in the treatment of urinary incontinence in women, Prog. Urol. 13 (656-9) (Sept 2003).
[10] A. Mostafa, C.P. Lim, L. Hopper, P. Madhuvrata, M. Abdel-Fattah, Single-incision mini-slings versus standard midurethral slings in surgical management of female stress urinary incontinence: an updated systematic review and meta-analysis of effectiveness and complications, Eur. Urol. 65 (2) (2014) 402–427 (Internet, 2013/09/24 ed., Available from: http://www.ncbi.nlm.nih.gov/pubmed/24055431).
[11] M.O. Schimpf, D.D. Rahn, T.L. Wheeler, M. Patel, A.B. White, F.J. Orejuela, et al., Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis, Am. J. Obstet. Gynecol. 211 (1) (2014) (2014/02/04 ed., 71 e1-71 e27).
[12] M.G. Lucas, R.J.L. Bosch, F.C. Burkhard, F. Cruz, T.B. Madden, A.K. Nambiar, et al., EAU guidelines on surgical treatment of urinary incontinence, Eur. Urol. 62 (2012) 1118–1129.
[13] K.L. Guerrero, S.J. Emery, K. Wareham, S. Ismail, A. Watkins, M.G. Lucas, A randomised controlled trial comparing TVT, Pelvicol and autologous fascial slings for the treatment of stress urinary incontinence in women, BJOG 117 (12) (2010 Nov) 1493–1502.
[14] F. Claerhout, G. Verbist, E. Verbeken, M. Konstantinovic, D. De Ridder, J. Deprest, Fate of collagen-based implants used in pelvic floor surgery: a 2-year follow-up study in a rabbit model, Am. J. Obstet. Gynecol. 198 (1) (Jan 2008) 94.e1–94.e6 (Internet, cited 2014 Jul 15, Available from: http://www.sciencedirect.com/science/article/pii/S0002937807006722).
[15] P.J. VandeVord, K.M. Broadrick, B. Krishnamurthy, A.K. Singla, A comparative study evaluating the in vivo incorporation of biological sling materials, Urology 75 (5) (May 2010) 1228–1233.
[16] J.S. Jones, R.R. Rackley, R. Berglund, J.B. Abdelmalak, G. DeOrco, S.P. Vasavada, Porcine small intestinal submucosa as a percutaneous mid-urethral sling: 2-year results, BJU Int. 96 (1) (Jul 2005) 103–106 (Internet, cited 2014 Jul 15, Available from: http://www.ncbi.nlm.nih.gov/pubmed/15963130).
[17] S. Siracusano, S. Ciciliato, N. Lampropoulou, A. Cucchi, F. Visalli, R. Talamini, Porcine small intestinal submucosa implant in pubovaginal sling procedure on 48 consecutive patients: long-term results, Eur. J. Obstet. Gynecol. Reprod. Biol. 158 (2) (Oct 2011) 350–353 (Internet, cited 2014 Jul 16, Available from: http://www.sciencedirect.com/science/article/pii/S0301211511003708).
[18] K.-L.V. Ho, M.N. Witte, E.T. Bird, 8-ply small intestinal submucosa tension-free sling: spectrum of postoperative inflammation, J. Urol. 171 (1) (Jan 2004) 268–271 (Internet, cited 2014 Jul 15, Available from: http://www.ncbi.nlm.nih.gov/pubmed/14665891).
[19] D. Kwon, Y. Kim, R. Pruchnic, R. Jankowski, I. Usiene, F. de Miguel, et al., Periurethral cellular injection: comparison of muscle-derived progenitor cells and fibroblasts with regard to efficacy and tissue contractility in an animal model of stress urinary incontinence, Urology 68 (2) (Aug 2006) 449–454 (Internet, cited 2012 Jun 6, Available from: http://www.ncbi.nlm.nih.gov/pubmed/16904482).
[20] C.-S. Lin, T.F. Lue, Stem cell therapy for stress urinary incontinence: a critical review, Stem Cells Dev. 21 (6) (Apr 10 2012) 834–843 (Internet, cited 2012 Jun 6, Available from: http://www.ncbi.nlm.nih.gov/pubmed/22121849).
[21] H. Ning, M. Albersen, G. Lin, T.F. Lue, C.-S. Lin, Effects of EdU labeling on mesenchymal stem cells, Cytotherapy [Internet]15(1), Elsevier Inc., Jan 2013. 57–63 (cited 2014 Jul 21, Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3535288&tool=pmcentrez&rendertype=abstract).
[22] G. Lin, G. Wang, L. Banie, H. Ning, A.W. Shindel, T.M. Fandel, et al., Treatment of stress urinary incontinence with adipose tissue derived stem cells, Cytotherapy 12 (1) (2010) 88–95.
[23] H. Thaker, A.K. Sharma, Regenerative medicine based applications to combat stress urinary incontinence, World J. Stem Cells 5 (4) (Oct 26 2013) 112–123 (Internet, cited 2014 Jul 22).
[24] C. Dissaranan, M.A. Cruz, M.J. Kiedrowski, B.M. Balog, B.C. Gill, M.S. Penn, et al., Rat mesenchymal stem cell secretome promotes elastogenesis and facilitates recovery from simulated childbirth injury, Cell Transplant. (Jul 17 2013) 1–32 (Internet, cited 2014 Jul 21, Available from: http://www.ncbi.nlm.nih.gov/pubmed/23866688).
[25] C. Dissaranan, E. Holthaus, M. Cruz, B. Balog, M. Kiedrowski, M. Penn, et al., 120 mesenchymal stem cell (Msc) secreted factors facilitate pudendal nerve (Pn) recovery after simulated childbirth injury, J Urol [Internet], 187(4), Elsevier Inc., Apr 2012. e48–e49 (cited 2012 Jun 6, Available from: http://linkinghub.elsevier.com/retrieve/pii/S0022534712005289).
[26] M. Vaegler, A.T. Lenis, L. Daum, B. Amend, A. Stenzl, P. Toomey, et al., Stem cell therapy for voiding and erectile dysfunction, Nat Rev Urol [Internet], 9(8), Nature Publishing Group, 2012. 435–447 (Available from: http://dx.doi.org/10.1038/nrurol.2012.111).
[27] M. Blaganje, A. Lukanović, Intrasphincteric autologous myoblast injections with electrical stimulation for stress urinary incontinence, Int J Gynaecol Obstet [Internet], 117(2), International Federation of Gynecology and Obstetrics, May 2012. 164–167 (cited 2012 Jun 6, Available from: http://www.ncbi.nlm.nih.gov/pubmed/22342057).
[28] C.J. Chermansky, T. Tarin, D.-D. Kwon, R.J. Jankowski, T.W. Cannon, W.C. de Groat, et al., Intraurethral muscle-derived cell injections increase leak point pressure in a rat model of intrinsic sphincter deficiency, Urology 63 (4) (Apr 2004) 780–785 (Internet, cited 2012 Mar 16, Available from: http://www.ncbi.nlm.nih.gov/pubmed/15072911).
[29] T.W. Cannon, J.Y. Lee, G. Somogyi, R. Pruchnic, C.P. Smith, J. Huard, et al., Improved sphincter contractility after allogenic muscle-derived progenitor cell injection into the denervated rat urethra, Urology 62 (5) (Nov 2003) 958–963 (Internet, cited 2012 Jun 6, Available from: http://linkinghub.elsevier.com/retrieve/pii/S0090429503006794).
[30] M.C. Heidekamp, F.C. Leong, L. Brubaker, B. Russell, Pudendal denervation affects the structure and function of the striated, urethral sphincter in female rats, Int. Urogynecol. J. 9 (1998) 88–93.
[31] A.S. Lin, S. Carrier, D.M. Morgan, T.F. Lue, Effect of simulated birth trauma in the urinary continence mechanism in the rat, Urology 52 (1) (1998) 143–151.
[32] T.W. Cannon, E.M. Wojcik, C.L. Ferguson, S. Saraga, C. Thomas, M.S. Damaser, Effects of vaginal distension on urethral anatomy and function, BJU Int. 90 (4) (2002) 403–407 (Internet, Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12175397).
[33] M.S. Damaser, C. Broxton-King, C. Ferguson, F.J. Kim, J.M. Kerns, Functional and neuroanatomical effects of vaginal distention and pudendal nerve crush in the female rat, J. Urol. 170 (3) (Sep 2003) 1027–1031 (Internet, cited 2012 May 3, Available from: http://linkinghub.elsevier.com/retrieve/pii/S0022534705633010).
[34] A. Hijaz, F. Daneshgari, K.-D. Sievert, M.S. Damaser, Animal models of female stress urinary incontinence, J. Urol. 179 (6) (Jun 2008) 2103–2110 (Internet, cited 2012 Mar 19, Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2596910&tool=pmcentrez&rendertype=abstract).
[35] H.H. Jiang, M.S. Damaser, Animal Models of Stress Urinary Incontinence, in: K.-E. Andersson, M.C. Michel (Eds.), The Handbook of Experimental Pharmacology, Urinary Tract, Vol 202, 2011 (Available from: http://dx.doi.org/10.1007/978-3-642-16499-6).

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[36] K.P. Sajadi, D.L. Lin, J.E. Steward, B. Balog, C. Dissaranan, P. Zaszczurynski, et al., Pudendal Nerve Stretch Reduces External Urethral Sphincter Activity in Rats, JURO [Internet], 188(4), Elsevier Inc., 2012. 1389–1395 (Available from: http://dx.doi.org/10.1016/j.juro.2012.06.006).
[37] L.L. Woo, A. Hijaz, H.Q. Pan, M. Kuang, R.R. Rackley, M.S. Damaser, Simulated Childbirth Injuries in an Inbred Rat Strain, 3612009. 356–361 (October 2008).
[38] D. Eberli, K.-E. Andersson, J.J. Yoo, A. Atala, A canine model of irreversible urethral sphincter insufficiency, BJU Int. 103 (2) (Jan 2009) 248–253 (Internet, cited 2012 Jun 6, Available from: http://www.ncbi.nlm.nih.gov/pubmed/18782310).
[39] S. Badra, K.-E. Andersson, A. Dean, S. Mourad, J.K. Williams, Long-term structural and functional effects of autologous muscle precursor cell therapy in a nonhuman primate model of urinary sphincter deficiency, J. Urol. 190 (5) (Nov 2013) 1938–1945 (Internet, cited 2014 Jul 13, Available from: http://www.ncbi.nlm.nih.gov/pubmed/23618586).
[40] K.D. Sievert, M.E. Bakircioglu, T. Tsai, S.E. Dahms, L. Nunes, T.F. Lue, The effect of simulated birth trauma and/or ovariectomy on rodent continence mechanism. Part I: functional and structural change, J. Urol. 166 (1) (Jul 2001) 311–317 (Internet, Available from: http://www.ncbi.nlm.nih.gov/pubmed/11435892).
[41] H.Q. Pan, J.M. Kerns, D.L. Lin, S. Liu, N. Esparza, M.S. Damaser, Increased duration of simulated childbirth injuries results in increased time to recovery, Am. J. Physiol. Regul. Integr. Comp. Physiol. 292 (4) (Apr 2007) R1738–R1744 (Internet, cited 2012 Mar 22, Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2536599&tool=pmcentrez&rendertype=abstract).
[42] H.Q. Pan, J.M. Kerns, D.L. Lin, D. Sypert, J. Steward, C.R.V. Hoover, et al., Dual simulated childbirth injury delays anatomic recovery, Am. J. Physiol. Ren. Physiol. 296 (2) (Feb 2009) F277–F283 (Internet, cited 2012 Jun 6, Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2643865&tool=pmcentrez&rendertype=abstract).
[43] H. Jiang, H.Q. Pan, M.A. Gustilo-ashby, B. Gill, J. Glaab, P. Zaszczurynski, et al., Dual simulated childbirth injuries result in slowed recovery of pudendal nerve and urethral function, Neurourol. Urodyn. 28 (2009) 229–235.
[44] G. Wang, G. Lin, H. Zhang, X. Qiu, H. Ning, L. Banie, et al., Effects of prolonged vaginal distension and β-aminopropionitrile on urinary continence and urethral structure, Urology [Internet], 78, Elsevier Inc., Oct 2011. 968.e13–968.e19 (cited 2012 Jun 6, Available from: http://www.ncbi.nlm.nih.gov/pubmed/21982017).
[45] Q. Song, B.M. Balog, J. Kerns, D.L. Lin, Y. Sun, M.S. Damaser, et al., Long-Term Effects of Simulated Childbirth Injury on Function and Innervation of the Urethra, 2014. (October 2013).
[46] X.-W. Du, H.-L. Wu, Y.-F. Zhu, J.-B. Hu, F. Jin, R.-P. Lv, et al., Experimental study of therapy of bone marrow mesenchymal stem cells or muscle-like cells/calcium alginate composite gel for the treatment of stress urinary incontinence, Neurourol Urodyn [Internet], 32(3), Wiley Subscription Services, Inc., A Wiley Company, Mar 1 2013. 281–286 (cited 2014 Jul 13, Available from: http://onlinelibrary.wiley.com/doi/10.1002/nau.22291/full).
[47] T.W. Cannon, M.S. Damaser, Effects of anesthesia on cystometry and leak point pressure of the female rat, Life Sci. 69 (10) (Jul 27 2001) 1193–1202 (Internet, Available from: http://www.ncbi.nlm.nih.gov/pubmed/11508351).
[48] H.-H. Jiang, A.M. Gustilo-Ashby, L.B. Salcedo, H.Q. Pan, D.F. Sypert, R.S. Butler, et al., Electrophysiological function during voiding after simulated childbirth injuries, Exp Neurol, 215(2), Elsevier B.V., Feb 2009. 342–348 (cited 2012 Oct 24, Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2721825&tool=pmcentrez&rendertype=abstract).
[49] A.J. Shoffstall, P.J. Zaszczurynski, R.S. Butler, M.S. Damaser, Development of a device to standardize leak point pressure experiments in rats, Neurourol. Urodyn. 27 (6) (2008) 553–558.
[50] L. Hakim, M. Endoh, A. Feola, D.M. Soebadi, J. Deprest, D. De Ridder, et al., High-frequency micro-ultrasound: a novel method to assess external urethral sphincter function in rats following simulated birth injury, Neurourol. Urodyn. (Jan 2014).
[51] M. Aref-Adib, B.W. Lamb, H.B. Lee, E. Akinnawo, M.M. a Raza, A. Hughes, et al., Stem cell therapy for stress urinary incontinence: a systematic review in human subjects, Arch. Gynecol. Obstet. 288 (6) (Dec 2013) 1213–1221 (Internet, cited 2014 Jul 16, Available from: http://www.ncbi.nlm.nih.gov/pubmed/24077813).
[52] M.B. Chancellor, T. Yokoyama, S. Tirney, C.E. Mattes, H. Ozawa, N. Yoshimura, et al., Preliminary results of myoblast injection into the urethra and bladder wall: a possible method for the treatment of stress urinary incontinence and impaired detrusor contractility, Neurourol. Urodyn. 19 (3) (Jan 2000) 279–287 (Internet, Available from: http://www.ncbi.nlm.nih.gov/pubmed/10797585).
[53] M. Mitterberger, R. Marksteiner, E. Margreiter, G.M. Pinggera, D. Colleselli, F. Frauscher, et al., Autologous myoblasts and fibroblasts for female stress incontinence: a 1-year follow-up in 123 patients, BJU Int. 100 (5) (Nov 2007) 1081–1085 (Internet, cited 2012 Jun 6, Available from: http://www.ncbi.nlm.nih.gov/pubmed/17760890).
[54] P. Sèbe, C. Doucet, J.-N. Cornu, C. Ciofu, P. Costa, S.G.D. de Medina, et al., Intrasphincteric injections of autologous muscular cells in women with refractory stress urinary incontinence: a prospective study, Int. Urogynecol. J. 22 (2) (Feb 2011) 183–189 (Internet, cited 2012 Jun 6, Available from: http://www.ncbi.nlm.nih.gov/pubmed/20821309).
[55] L.K. Carr, D. Steele, S. Steele, D. Wagner, R. Pruchnic, R. Jankowski, et al., 1-Year follow-up of autologous muscle-derived stem cell injection pilot study to treat stress urinary incontinence, Int. Urogynecol. J. Pelvic Floor Dysfunct. 19 (6) (Jun 2008) 881–883 (Internet, cited 2014 Jul 16, Available from: http://www.ncbi.nlm.nih.gov/pubmed/18204978).
[56] C.N. Lee, J.B. Jang, J.Y. Kim, C. Koh, J.Y. Baek, K.J. Lee, Human cord blood stem cell therapy for treatment of stress urinary incontinence, J. Korean Med. Sci. 25 (6) (Jun 2010) 813–816 (Internet, cited 2012 Jun 6, Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2877237&tool=pmcentrez&rendertype=abstract).
[57] L.K. Carr, M. Robert, P.L. Kultgen, S. Herschorn, C. Birch, M. Murphy, et al., Autologous muscle derived cell therapy for stress urinary incontinence: a prospective, dose ranging study, J Urol [Internet], 189(2), Elsevier Inc., Feb 2013. 595–601 (cited 2014 Jul 21, Available from: http://www.ncbi.nlm.nih.gov/pubmed/23260547).
[58] K. Kuismanen, R. Sartoneva, S. Haimi, B. Mannerström, E. Tomás, S. Miettinen, et al., Autologous adipose stem cells in treatment of female stress urinary incontinence: results of a pilot study, Stem Cells Transl. Med. 3 (8) (2014) 936–941 (Internet, cited 2014 Jul 13; Available from: http://www.ncbi.nlm.nih.gov/pubmed/24985079).
[59] X.H. Zou, Y.L. Zhi, X. Chen, H.M. Jin, L.L. Wang, Y.Z. Jiang, et al., Mesenchymal stem cell seeded knitted silk sling for the treatment of stress urinary incontinence. Biomaterials [Internet]. Elsevier Ltd; 2010 Jun [cited 2014 Jul 13]; 31(18):4872–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20303586.
[60] W. Zhao, C. Zhang, C. Jin, Z. Zhang, D. Kong, W. Xu, et al., Periurethral injection of autologous adipose-derived stem cells with controlled-release nerve growth factor for the treatment of stress urinary incontinence in a rat model, Eur Urol [Internet], 59(1), European Association of Urology, Jan 2011. 155–163 (cited 2012 Mar 1, Available from: http://www.ncbi.nlm.nih.gov/pubmed/21050657).
[61] A.K. Sharma, M.I. Bury, N.J. Fuller, D.I. Rozkiewicz, P.V. Hota, D.M. Kollhoff, et al., Growth factor release from a chemically modified elastomeric poly(1,8-octanediol-co-citrate) thin film promotes angiogenesis in vivo, J. Biomed. Mater. Res. A 100 (3) (Mar 2012) 561–570 (Internet, cited 2014 Jul 23, Available from: http://www.ncbi.nlm.nih.gov/pubmed/22162300).
[62] T.W. Cannon, D.D. Sweeney, D.A. Conway, I. Kamo, N. Yoshimura, M. Sacks, et al., A tissue-engineered suburethral sling in an animal model of stress urinary incontinence, BJU Int. 96 (2005) 664–669.
[63] A. Mangera, A.J. Bullock, S. Roman, C.R. Chapple, S. MacNeil, Comparison of candidate scaffolds for tissue engineering for stress urinary incontinence and pelvic organ prolapse repair, BJU Int. 112 (5) (Sep 2013) 674–685 (Internet, cited 2014 Jul 13, Available from: http://www.ncbi.nlm.nih.gov/pubmed/23773418).
[64] S. Roman, A. Mangera, N.I. Osman, A.J. Bullock, C.R. Chapple, S. MacNeil, Developing a tissue engineered repair material for treatment of stress urinary incontinence and pelvic organ prolapse-which cell source? Neurourol. Urodyn. 33 (5) (Jun 2014) 531–537 (Internet, cited 2014 Jul 13, Available from: http://www.ncbi.nlm.nih.gov/pubmed/23868812).
[65] M.L. Hart, K.M.H. Neumayer, M. Vaegler, L. Daum, B. Amend, K.D. Sievert, et al., Cell-based therapy for the deficient urinary sphincter, Curr. Urol. Rep. 14 (5) (Oct 2013) 476–487 (Internet, cited 2014 Jul 13, Available from: http://www.ncbi.nlm.nih.gov/pubmed/23824516).

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